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Progress report: Pittsburgh Breast Cancer Consortium:

Principal Investigator: Adam Brufsky, MD, PhD

Introduction:

The University of Pittsburgh Cancer Institute, the Magee-Women's Hospital, the Hematology-Oncology Associates of the UPCI (HOA), the Pittsburgh Clinical Research Network, Inc. (PCRN), the Magee Womancare Breast Cancer Volunteer Program, and the Pittsburgh Branch of the National Association for the Advancement of Colored People (NAACP) are collaborating to form the Pittsburgh Breast Cancer Consortium (PBCC). The focus of this partnership is the rapid clinical development of new agents for the treatment of metastatic breast cancer (MBC). The PBCC will conduct innovative phase I and phase II clinical trials testing new approaches in the treatment of MBC. Accrual to these trials will derive from a consortium of Pittsburgh regional, community based oncology practices of the HOA in collaboration with the Magee-Women's Hospital/University of Pittsburgh Cancer Institute Comprehensive Breast Cancer Center (CBCC). The Consortium will be centered at the University of Pittsburgh Cancer Institute (UPCI), an NCI-designated Comprehensive Cancer Center. The UPCI, which has an outstanding clinical trials support infrastructure, will provide the template for development of central data management, coordination oversight, trials auditing, biostatistical support, pharmacokinetic analysis, and interaction with industrial partners. The PBCC will establish the mechanisms for the conduct of new studies, with a strong emphasis on community-based practice involvement. In addition, the PBCC will be overseen and advised by a central governing board for the Consortium, meeting monthly, composed of representatives of the UPCI, the HOA, the PCRN, the volunteer group, and the NAACP.

The specific aims of this proposal are (1) to develop a breast cancer clinical trials infrastructure to allow the rapid phase I and phase II development of novel agents for the treatment of breast cancer with a strong emphasis on community-based practice involvement; and (2) to evaluate multiple agents, as well as combinations of agents, using this infrastructure.

In this progress report, we will detail how our objectives to date have been met. The workstatement will be used as a template. To briefly summarize, we continue to build the infrastructure of the PBCC and are currently conducting clinical trials of novel agents and combinations of agents. As noted in the original proposal, priorities of industrial sponsors change, as do the availability of agents. While we have not conducted all of the proposed clinical trials, other trials have been and are currently being conducted in the PBCC.

Body:

Statement of Work:

Task 1: Develop the PBCC Infrastructure (Months 1-12)

- Recruit and train nurse-coordinators. This has been done. Our governing committee decided that the best method of increasing community nurse coordinator support of PBCC clinical trials would be to buy time from existing community coordinators. The PBCC now pays for three full time coordinators at the central site at Magee-Women's Hospital as well a 2/9 FTE of each of nine community coordinators. Each of the coordinators is expected to accrue 9-12 patients per year onto PBCC clinical trials to continue receiving support.
- Recruit and train data managers. This has been done. There are currently two data managers supported by the PBCC working at Magee-Women's Hospital.
- Educate community oncologists about the PBCC. Community oncologist education continues. Dr. Brufsky continues to meet quarterly with small groups (6-10) community oncologists to discuss PBCC trials and accrual goals. In May 2003, prior to the Koman Race for the Cure in Pittsburgh, a marketing company retained by the PBCC (Jack Horner Communications) announced our consortium to the lay public of Pittsburgh. A brochure describing the PBCC with a logo specific to the PBCC has been created. Physicians participating in the PBCC are currently receiving wall plaques to be displayed in their offices announcing their participation. The PBCC has also retained a web design company (GIST) to build and maintain a PBCC web site for physicians and lay public. The content of this website is currently available (website address), and is continually updated by GIST.
- Initiate PBCC governing board and set schedule of meetings. We currently meet bimonthly. The current composition of the board is Adam Brufsky, MD, PhD; Merrill Egorin, MD; Ron Herberman, MD; Lyn Robertson, MSN; Barry Lembersky, MD; Sam Jacobs, MD; Victor Vogel, MD; and representing the patients, Kathy Purcell, MSW, and Anne Humphries, MS.
- Initiate protocol processing through the PCRN and IRB. This has been done. Two trials from the Lilly Corporation have been initiated through PCRN solely, and at least ten trials for MBC have been initiated in total since the start of funding.
- Test existing UPCI-Based Intranet and PCRN protocol Web server and develop PBCC Web site. GIST corporation has taken the lead in developing the PBCC Web site (which went active in September 2002, and is updated monthly). The protocol Web server should be complete by June 2004.

Task 2: Evaluation of Novel Compounds for the Treatment of Metastatic Breast Cancer (MBC) in the PBCC (Months 1-36) (As noted above, certain protocols were not initiated and were replaced during the first 18 months of this award)

- Phase I trial of 17-AAG (anti-HSP 90). This trial was completed, and results were presented at ASCO 2003. A manuscript is currently in preparation.

- Phase II trial of L-778,123 (farnesyltransferase inhibitor) in MBC. This trial was completed. A manuscript is currently in preparation.
- Phase II trial of oral dexamethasone and calcitriol in MBC. Due to the departure of Dr. Trump from the UPCI, this trial will not be performed.
- Phase II trial of MUC-1 peptide vaccination in women with MBC. This trial is continues in development with Dr. Olga Finn and Dr. Joseph Baar, and will likely open in the 2nd Quarter of 2004.
- Phase II trial of trastuzumab and tamoxifen in tamoxifen-resistant MBC. This trial continues on hold by the sponsor (Genentech).

Other current trials performed by the PBCC:

- Phase II trial of Carboplatin/taxotere in MBC (Aventis). This trial was added to the PBCC in October 2000, and accrual thereafter was rapid. This trial was completed in December 2001, and presented at ASCO 2002. A manuscript will be submitted for publication shortly.
- Phase II trial of Carboplatin/taxotere/Herceptin in MBC (Aventis). This trial was added to the PBCC in October 2000, and accrual thereafter was also rapid. This trial was completed in September 2002, and was presented at ASCO 2003. A manuscript will be submitted for publication shortly.
- A phase II, Multicenter, Randomized, Open-Label, Dose Comparison Study of Recombinant Human Chorionic Gonadotropin for Third Line Treatment of Metastatic Breast Cancer in Postmenopausal Women (Ares-Serono). We accrued 12 patients in the PBCC (12% of total) in this Multicenter trial. The trial is complete, and a manuscript will be submitted for publication shortly.
- A multicenter, open-label, phase III, randomized, active-controlled trial evaluating the efficacy, safety, and pharmacokinetics of rhuMAb VEGF, in combination with capecitabine chemotherapy, in subjects with previously treated metastatic breast cancer (Genentech). The PBCC accrued 10 patients on this Multicenter phase II study. This trial is currently complete. Data for the multicenter trial were presented at the San Antonio Breast Symposium 2002.
- Phase II trial of Gemcitabine/Herceptin in MBC (Lilly). This multicenter trial was brought to the PBCC by the PCRN in March 2002. This trial is continuing, with the PBCC responsible for 18 of the 42 accruals nationally.
- Phase II Trial of Randomized Trial of Gemcitabine Plus Docetaxel vs. Docetaxel Plus Capecitabine in Metastatic Breast Cancer in 1st and 2nd Line Patients. This multicenter trial was also brought to the PBCC by the PCRN in March 2002. This trial is continuing, with the PBCC responsible for 13 of the 151 accruals nationally.
- A Phase II Clinical Trial of BMS-247550 (NSC 710428), an Epothilone B Analog, in Patients with Breast Cancer (NCI). The PBCC initiated this trial in May 2003. This trial continues, with the PBCC accruing 8 of the 45 patients nationally.
- A Phase I Trial Evaluating the Safety of Intramuscular Injection of HER-2 Protein Autovac in Patients with Brest Cancer (Pharmexa). This trial was initiated in June 2003. The PBCC accrued 5 of the planned 11 patients. This trial is now complete, and results will be presented at the European Breast Cancer Conference in Copenhagen in February 2004.

- A Phase I Dose-Escalation Study of Thrice Weekly Recombinant Human Interleukin-2 in Combination with Trastuzumab in Subjects with Her2/neu Positive Metastatic Breast Cancer (Chiron). This trial opened in January 2003. The PBCC accrued 4 of the 14 patients enrolled nationally. This trial is now closed, and results were presented at the San Antonio Breast Symposium 2003.

The PBCC plans on several trials to open in the next 1-2 months specific to refractory MBC. These include:

1. A phase II trial of a novel oral inhibitor of the tyrosine kinase associated with Her2 Neu (GlaxoWellcome);
2. A phase II trial to individually characterize chemoresistance in women with MBC, using a novel chemosensitivity assay and cDNA expression profiling (Precision Therapeutics, Incorporated);
3. A phase II trial of Amonafide: Individual phenotype-adjusted chemotherapy for women with metastatic breast cancer who have progressed despite prior chemotherapy;
4. An Open Label Phase II Study of E7070 (novel microtubule inhibitor) in Metastatic Breast Cancer Patients Previously Treated with an Anthracycline, a Taxane and Capecitabine;
5. A phase II study of a kinesin inhibitor in previously treated women with metastatic breast cancer;
6. A Phase II Trial of Novel Epothilone BMS-247550 in Patients with Advanced Breast Cancer Who are Resistant to an Anthracycline, a Taxane and Capecitabine.

Task 3: Dissemination of Research Results (Months 18-36)

- Presentation of PBCC infrastructure results to USAMRMC-BCRP Symposium (Month 24). Dr. Brufsky will attend the DOD meeting in September 2004 to present results.
- Preparation and publication of results from clinical studies from months 1-24 (Months 24-36). This is currently underway as noted above.
- Visits to the PBCC for industry representatives, faculty, and community physicians (Months 18-36). This is also currently underway as noted above. Dr. Brufsky presented results of the PBCC infrastructure to the Pennsylvania Breast Cancer Coalition Annual Meeting in Harrisburg, PA on October 8, 2003. In addition, Dr. Brufsky gave a presentation to the Pittsburgh community on the PBCC in Greensburg, PA on October 23, 2003.

Key Research Accomplishments:

- Recruited and trained 3 nurse coordinators and 2 data managers
- Assembled PBCC governing board
- Developed PBCC Web site
- Completed or assisted in completion of six phase I and phase II clinical trials in refractory, metastatic breast cancer with substantial community involvement and accrual

Reportable Outcomes:

Brufsky A, Matin K, Baar J, Cleary D, Lebish J, Jacobs S, Belani C. A phase II study of carboplatin and docetaxel as first line chemotherapy in metastatic breast cancer. Proc ASCO 2002; 21: 2020a.

Brufsky A, Cleary D, Jacobs S, Baar J, Belani C. First-line chemotherapy for metastatic breast cancer (MBC) with docetaxel (T), carboplatin (C), and trastuzumab (H) (TCH) : a phase II trial. Proc ASCO 2003; 22:71a

Chang JC, Kalidas M, Zhou L, Yu S, Cate E, Lowe A, Wilson S, Bedell L, Milan S, **Brufsky A**, Garino LA, Miller J, Hutchins L, Lee M. Interleukin-2 and trastuzumab: preliminary results in clinical response and natural killer cell expansion in advanced Her2/neu positive metastatic breast cancer patients. Breast Cancer Treat Res 2004; 21:220a

Overmoyer B., **Brufsky A.**, Volck B., Leach D., Østergaard A. A phase I trial evaluating the safety and immunogenicity of a HER-2 protein vaccine in patients with breast cancer. Proc ECCO 2004.

Low JA, Wedam SB, **Brufsky A**, Berman A, Croarkin E, Parks R, Steinberg S, Mannan N, Fojo T, Swain S. A phase 2 trial of BMS-247550 (ixabepilone), an epothilone B analog, given daily x 5 in breast cancer. Proc ASCO 2004.

Conclusions:

The PBCC has had a very successful year in the rapid accrual to multiple phase I and phase II trials for refractory, metastatic breast cancer and provides an excellent example of a successful community-academic partnership. In the subsequent year of this proposal, we will continue to initiate and to accrue to multiple phase I and phase II trials of novel therapies for metastatic breast cancer. We will also continue to disseminate our results at national meetings and in clinical research journals. Finally, we will present our experience with forming the PBCC infrastructure at a national meeting this year.